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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,926	11/13/2003	Pavel Slanina	SYN-0036	7713

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SYNTHON IP INC
7130 HERITAGE VILLAGE PLAZA
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GAINESVILLE, VA 20155

EXAMINER

MOORE, SUSANNA

ART UNIT	PAPER NUMBER
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1624

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/705,926

Applicant(s)

SLANINA ET AL.

Examiner

Susanna Moore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 January 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's arguments, see Remarks, filed 1/16/2007, with respect to Office Action mailed 7/14/2006 have been fully considered. Some of the rejections have been withdrawn and others have been maintained. In summary, claims 1-13 are pending and claims 1-13 stand rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9-11, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Marquillas Olondriz et. al. (ES 2050069).

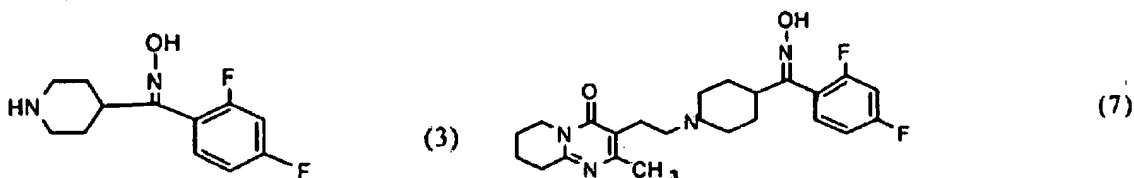
Marquillas Olondriz et. al. teaches the reaction of the oxime intermediate 7 to the cyclized product, risperidone, with sodium in refluxing THF. See column 6, example 9, lines 60-67, and column 7, lines 1-28, and the final cyclized product, column 7, example 10, lines 30-47 and column 8, lines 1-15.

In addition, Marquillas Olondriz et. al. must have had the oxime enriched with the Z-isomer to obtain a yield of 87.7% of the cyclized product. Applicant discloses on page 7 of the

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Specification that the E-isomer is “unreactive” due to the orientation of the hydroxyl group pointing away from the fluoro substituent. Thus, the Z-isomer must have been present in the oxime mixture in excess of 90%, since most cyclized reactions do not go to 100% yield.

The rejected claims are drawn to the enriched Z-isomer oxime 7 in greater than 80% yield.



The Specification on page 10 states, “An enriched Z-isomer oxime of formula (3) and (7) can also be obtained by conversion of the E-isomer oxime into the Z-isomer form. Specifically, by heating the E-isomer, typically a mixture of the Z- and E-isomers, in a solvent, the E-isomer is converted into the Z-isomer. More specifically, the undesired E-isomer is converted into the E-isomer of the oxime...by heating in an inert solvent...at a sufficient temperature, preferably, higher than 80°C.”

The Specification also states on page 7, “Because of the discovery that the E-isomer oxime is not merely slower reacting than the Z-isomer oxime but rather is essentially unreactive,....”

As the Specification says the enrichment occurs on “heating in an inert solvent,” this heating inherently produces the enrichment.

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Applicant argues that the Z-isomer may not have been present in excess of 90% due to “equilibrium forces surrounding the conversion to (isomerization) and reaction (cyclization) of the Z-isomer.” Applicants recited the below paragraph:

The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. “The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness.” *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983).

Applicants also go on to recite *In re Rijckaert*, *In re Oelrich* and *In re Robertson* stating,

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). “To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.” *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

The Examiner provided the rationale, which was stated above, showing inherency based on the yield of the reaction and the fact that the E-isomer is unreactive. Since the reference is silent on the property of the % enrichment of the Z-isomer Applicants argument may be correct that the Z-isomer may not have been present in such high amounts. Due to the high yield of the reaction (84.7%), there is a reasonable basis to believe the amount of Z-isomer was not enriched greater than 95%. This is not an ordinary case of inherency since the same compound is present.

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overcome this reasonable basis with actual data, and not the mere possibility that the Examiner might be wrong.

Claims 9-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Kennis et. al. (US 4,804,663).

Kennis et. al. teaches the synthesis of oxime 3 under basic conditions in refluxing water followed by the cyclization of oxime 3. See column 11, lines 1-17 and column 12, lines 10-25.

The inherency argument mentioned above applies here as well. Thus, claims 9-12 are anticipated by Kennis et. al.

Applicants mention two arguments which need to be addressed. The first is, which sample needs to be analyzed according to the reference? The reference isolated, upon cooling, the precipitated product from the reaction mixture. Thus, the solid product of both experiments analyzed by Applicant shows a 95% enrichment of the Z-isomer.

The second argument made by Applicants, which needs to be addressed, is the fact that only the HCl salt of the oxime was isolated upon repeating the experiment twice. Applicants have note this is the wrong material since Applicants are claiming the acetic acid salt and the free amine. Note, the reference does not report the compounds as HCl salts. To address the issue at hand, Applicant has provided experimental data in their "Remarks" but this data can only be accepted in the form of a declaration. A declaration, not merely remarks, that shows the exact repeated experimental procedure and data indicating the Kennis experiments only produced an

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HCl salt of the intermediate compounds will overcome this rejection since this is not explicitly found in the reference.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strupczewski et. al. (U.S. 4,408,054).

The current invention teaches the process of making and use of acetic acid salts of oximes (3) and (7).

Strupczewski et. al. teaches compounds of salts of oxime (3). The compound 4-(2,4-difluorobenzoyl)-piperidine oxime is used in example 25, column 26, lines 66-67. This oxime intermediate is used for the exact same utility, the cyclization to the corresponding benzoisoxazole.

The difference between the prior art and the current invention is that the prior art reference uses the free base of compound (3) while Applicant uses the acetic acid salt of compound (3).

Claim 1 of the prior art references claims the oxime (3) "or salts thereof." See paragraph bridging columns 38 and 39. The only definition of salts is found in column 10, lines 61-68 of the patent, which lists 9 different pharmaceutically acceptable salts. Acetic acid is one of the salts mentioned, and therefore, acetic acid would be an obvious choice to use for compound (3).

The compound, 4-(2,4-difluorobenzoyl)-piperidine oxime, is used for the same utility in the reference as in the current invention, the synthesis of risperidone. The same sequence of reactions occurs, where the oxime is cyclized intramolecularly to the benzoisothiazole in refluxing water as the solvent. See column 27, lines 16-39. This heating does the enrichment.

The inherency argument mentioned above applies here as well. Thus, claims 1-8 are obvious over the teachings of Strupczewski et. al.

Applicants argue that example 25 in the reference is not cyclized to form the corresponding benzoisoxazole but in fact was used in an allylation reaction to form the allylated oxime reaction. This is true. The oxime of example 25 was used as a starting material in a different reaction but regardless of the use, the oxime (3) was example 25. This is the same oxime claimed in claim 1, oxime (3) as the acetic acid salt. Furthermore, the synthesis of the 2,6-dichloro oxime hydrochloride salt analog was pointed out to show how the 2,6-difluoro oxime (3) was made since the reference did not provide the experimental procedure for all the oximes made. Moreover, a global teaching of the pharmaceutically acceptable salts was pointed out in the '054 patent.

Applicants go on to argue that the pharmaceutically acceptable salts only corresponds to the final cyclized products, the benzoisoxazoles. This is not true. The patent states, "Preferred pharmaceutically acceptable salts include...." These salts are not limited only to the final products.

Regarding claims 4-8, since the same utility is addressed in the '054 patent, the same inherency argument provided above applies.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

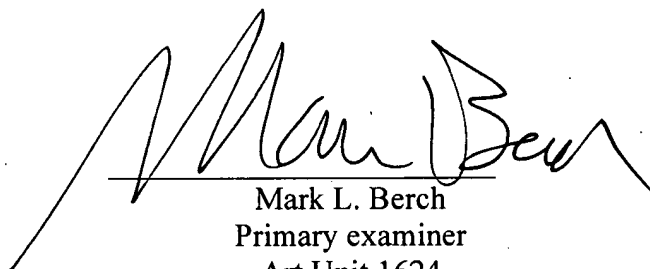
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susanna Moore whose telephone number is (571) 272-9046. The examiner can normally be reached on M-F 8:00-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SM
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